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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER	
WILLIAMS,J	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/02/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6/8/98.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 2-17, 19, 21, 23-33, 34-55 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 2-17, 19, 21, 23-33-34-55 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

DETAILED ACTION

Priority

1. This application is a National Stage Application filed under 35 U.S.C. § 371 and claims priority to PCT/US94/08825 filed 8/4/94.

Claim Status

2. The Preliminary Amendments has been received and made of record as Paper No. 13A. Claims 2-17, 19, 21, 23-33 and 34-55 are pending in this application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2-17, 19, 21, 23-33 and 34-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabled for immunizing against an infectious disease and against a chronic immune-mediated disorder in a mammal less than 96 months of age wherein the first dose begins within 42 days after birth wherein the immunogen is a combined anthrax vaccine and whole diptheria, tetanus vaccine (i.e., DPT) composition.

The broad claims encompass immunizing to prevent numerous infectious diseases and chronic immune mediated disorders by immunizing with a wide range of immunogens within the first 42 days of life. However, the specification is not considered enabled for this broad scope of the claims. ~~First off, the specification only demonstrates~~

To begin with, it is noted that art of preventing chronic immune mediated disorders (i.e., autoimmune disorders) is a highly unpredictable. Along these lines, it is well accepted in the art that the precise mechanisms by which the majority of autoimmune diseases arise remains unclear as evidenced by the

teaching of Miller et al. ("The Immune System and Microbe-Induced Autoreactive Host Responses and Autoimmune Disease" In: The Biological and Clinical Basis of Infectious Diseases, 5th edition, Shulman et al. eds., W.B. Saunders Company, Philadelphia, pages 15-28, 1997). Miller et al. at page 22 indicates that while it has been recognized for decades that autoimmune responses are often preceded by or associated with certain microbial infections, "the precise relationship between those cellular and/or humoral responses and the pathogenesis of self-tissue damage has been difficult to establish." Miller et al. further indicates that the existence of a tissue-reactive autoantibody in certain pathologic conditions does not confirm a causal relationship (also at page 22). In fact, Miller et al. states at page 22: "the autoantibody response may be an "epiphenomenon," secondary but unrelated to the disease pathology." Secondly, Miller et al. states at page 27 that "It is likely that multiple mechanisms of induction of anti-self-responses (e.g. molecular mimicry and epitope spreading), acting either alone or in concert, are operative in different autoimmune diseases." This is also evidence of the extreme difficulty and unpredictability in treatment for the broad spectrum of autoimmune diseases. For instance, it is well accepted that there is no specific therapy for multiple sclerosis and rheumatoid (i.e. two types autoimmune disease). Likewise, Adorini et al. (Trends in Immunology 18(5):209-211, 1997) clearly indicates that while cytokines and antigens are amongst the most popular targets and tools in the development of effective autoimmune immunotherapies, whether or not they can be translated into drugs still remains to be seen. Accordingly, it is unclear as to whether or not the full breadth of the claimed invention would have a positive effect as a preventative treatment for an autoimmune disease.

Secondly, it is noted that while there some exceptions as taught by the prior art below, the art of vaccinating new borns within the first six months of life is a highly unpredictable art. For instance, Spigland et a. (Pediatrics, May 1960, pages 812-821) teaches that the question of the earliest age to immunize is still a difficult question one to answer as evidenced by the data which indicate that 5- and 6-month-old infants respond better to primary immunization than do younger ones which is due, in part, to increased age and to

the frequency of absence of maternal antibodies which interfere with active antibody protectoin (page 819, 2nd col.).

It was also well known in the art at the time of filing that to date there are no vaccines for a number of the infectious viral conditions encompassed by the claims. For example, it is well accepted that there are numerous difficulties associated with treating HCV infection. For instance, Zuckerman et al. (J. Hepatology, 22(Suppl. 1):97-100, 1995) teach that to date effective neutralizing antibodies have not been identified (see page 100, top of first column), and that the high degree of genetic and serological heterogeneity of hepatitis C virus and reinfections will make the development of a broad spectrum effective hepatitis C vaccine difficult (see abstract). Moreover, Zuckerman et al. also teach that "reinfection with HCV occurs regularly following challenge, even if the subsequent challenge was with identical virus" (see page 99, top of first column). Since a previous natural HCV infection does not afford protection against subsequent re-infection, it is unclear whether a neutralized virus and/or neutralizing antibodies will afford protection. In addition, Zuckerman et al. further indicate that numerous viral types of HCV, as well as, numerous antibodies to HCV exist. Yet, as mentioned above, the disclosure fails to teach what virus was used, how it was treated/prepared, and what neutralizing antibodies were used in the PC. Nor does the disclosure demonstrate effective prevention of HCV infection and disease. Accordingly, claims which read on prevention of HCV infection are not enabled by such a teaching.

Likewise, claims directed to prevention of a wide variety of viral conditions such as those caused by the human immunodeficiency viruses, the herpesviruses, adenoviruses, papoviruses, parvoviruses, flaviviruses, etc., are also not enabled. For instance, it was well known in the art at the time of filing that no preventive vaccine for HIV infection exists and that there are numerous difficulties associated with the development of such a vaccine. Haynes's review (Science, Vol. 260, 1279-1286, 1993) teaches these difficulties which include: (1) the lack of an effective animal model which exactly mirrors human HIV

infection, (2) the lack of understanding about immune correlates of protection against HIV, (3) the incomplete understanding about HIV pathogenesis, (4) the existence of HIV protein sequence variability, especially in the principal neutralizing determinant, V3 loop region, of gp120, and (5) the need for anti-HIV mucosal immunity (see pages 1279-1281). Neither the specification nor the claims address any of these issues. Similarly, the development of a preventative herpesvirus vaccine, such as HSV-1 or HSV-2, is also complicated due to a lack of understanding about the protective immunological responses that follow infection. It was also well known in the art at the time of filing that HSV migrates by way of the axon to the sensory nerve nucleus of an infected cell where it can remain in a latent state for the life of the host. Thus, even though an immune response could be raised to a neutralized herpesvirus, the specification as well as the prior art fail to demonstrate that it would eradicate HSV reactivation and/or primary infection. Once again, the specification does not indicate how the claimed pharmaceutical compositions would overcome these problems. Accordingly, broad claims which encompass such viruses are not enabled.

Lastly, the specification is limited to a teaching which demonstrates vaccination with a combined anthrax-DPT vaccine and the effect it has on the onset of experimental diabetes in NOD mice, MRL mice, and BB rats (examples 1-5). For instance, Example 1 indicates that the cumulative incidence of diabetes in the anthrax treated group flattened out at 42.1% with no new cases detected after 24 weeks, plague vaccine flattened out at 57.9% diabetic at 28 weeks, and the control group showed a continual increase in the cumulative incidence of diabetes from 30% at 16 weeks to 65% at week 28 (Figure 1). Here the specification makes a case for mitigating the onset of diabetes with the anthrax vaccine administered at days 8, 15, and 29. Similarly, Example 2 shows similar results for a combined anthrax-DTP vaccine administered at days 1, 3, 10, week 4 and every 2 weeks through week 14. In this instance, none of the 29 animals developed diabetes at week 32 of age (Figure 2). While such results lend support to the early vaccination of a DPT-anthrax vaccine within the first 42 days of life to prevent diabetes in mice, it says nothing with regards to the *early*

vaccination (i.e., with the first 42 days of life) to prevent viral infections of the type mentioned in the preceding paragraphs. Nor does it speak to the difficulties in preventing other kinds of chronic immune mediated disorders. There is a dearth of guidance with respect to these other conditions and to early vaccination for these conditions. Nor does the disclosure demonstrate how to vaccinate in the manner suggested by the claims to treat or prevent against the wide variety of infectious diseases for which there are no known vaccines as discussed above.

Though one skilled in the art can readily formulate and use vaccines once efficacy has been demonstrated, this specification fails to provide results recognized in the art as reasonably predictive of vaccine efficacy for the full breadth of the claims. Without the demonstration of vaccine efficacy, one skilled in the art would have no reasonable ability to predict the outcome of the administration of the claimed pharmaceutical composition. Without the ability to predict vaccine efficacy, one skilled in the art has no way of calculating what dosage, method of administration, and frequency of administration is required to prevent, for instance, HIV, HCV, and HSV infection or disease induction or reactivation. Likewise, without the ability to predict therapeutic efficacy for a chronic immune mediated disorder, one skilled in the art has no way of calculating what dosage, method of administration, and frequency of administration is required to prevent "immunizing with an immunogen in such amounts and at such times as would substantially induce an immune-mediated disorder". Therefore, in view of the unpredictable nature of the art, the limited guidance in the specification, the lack of working examples with respect to the wide variety of infectious diseases, and the breadth of the claims, it would require an undue amount of experimentation to practice the invention within the full scope of the claims.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2-19, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terminology "substantially reduce the incidence or severity of such infectious disease" and "substantially reduce the incidence or severity of at least one chronic immune-mediated disorder" is vague and indefinite in that the metes and bounds of this language have not been defined. How much constitutes a substantial reduction. Does Applicant intend for prevention, treatment or both?

In claim 6 for example, the claim language "substantially greater" is vague and indefinite. The metes and bounds of this language have not been defined. How much is substantially greater?

In claim 31 for example, the claim terminology "specific times after birth" is vague and indefinite. What are these specific times?

In claim 2 for example, the claim terminology "immunizing with an immunogen in such amounts and at such times as would substantially induce an immune-mediated disorder"is vague and indefinite. What is this amount. Applicant has not demonstrated what constitutes "immunizing with an immunogen in such amounts and at such times as would substantially induce an immune-mediated disorder".

In claim 5 for example, the claim terminology "wherein one immunogen other than a BCG,...." is administered is vague and indefinite. Such claims fail to positively set forth what is claimed.

In claim 19 for example, the claim terminology "pediatric immunogen" and "non-pediatric immunogen" is vague and indefinite. What is a pediatric immunogen? What is a non-pediatric immunogen? How are they different? Are they different?

In claim 5, "BCG" is listed twice. If they are the same, then the claims is redundant. If not, then how are they different?

7. Claims 25-27 and 34-47, 49, and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims which are drawn to a product, i.e., a kit, have extensive intended-use limitations without actually stating the components of the kits. Does Applicant intend to claim a product or a method? If Applicant intends for a product claim to a kit, then Applicant should clearly set forth the components of the kits via positive limitations rather than intended-use limitations.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Kits = 8, 10, 11, 15, 16, 19 26-30 34-41, 43, 44, 46, 48-52, 55 New 56-100

9. Claims 2-4, 6-17, 19, 21, 23-33, 34-43 and 45-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Madore et al. (Pediatrics 85(3); 331-337, 1990). Method = 6, 21, 32, 33 New 101

Madore et al. teaches immunizing 1-month old infants (i.e., within the first 42 days of life) with a *Haemophilus influenza* type b oligosaccharide-CRM conjugate (i.e., a menigitis immunogen). Madore et al. further teaches that *Haemophilus influenza* type b is the cause of bacterial menigitis. (See abstract).

With regards to the kit claims, Applicant is reminded that though the claims include intended use limitations and/or other such functional language, the claims are interpreted without these limitations as a product (i.e., a pharmaceutical formulation containing the immunogen). In addition, the ability to prevent infectious diseases is considered an inherent property of the prior art immunogen in a pharmaceutical

formulation (i.e., kit).

3, 6, 8, 10, 11, 15, 16, 19, 26-30, 32-41, 43, 44, 46-52 New 56-101

10. Claims 2-4, 6-17, 19, 21, 23-33 and 34-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Dengrove et al. (Pediatric Research 20(8):745-739, 1986).

Dengrove et al. teaches DTP immunization in newborns and infants at 4 days of age in addition to the usual series at 2, 4, and 6 months of age (i.e., the first dose beginning before 42 days of age).

11. Claims 2-4, 6-17, 19, 21, 23-33 and 34-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Halsey et al. (Bulletin of the World Health Organization 63(6): 1151-1169, 1985).

Halsey et al. teaches immunization with a variety of vaccines within the 42 day window. For instance, Halsey et al. teaches vaccination with DPT at days 1-3, 5-8 (see Table 5) and at 4-8 weeks of age (page 1162, 2nd col.). Halsey et al. also teaches whole-cell pertussis vaccination at 1, 9, and 13 weeks demonstrated 64% protective efficacy (page 1162, 2nd col.). Halsey et al. further describes a study suggesting that improved protection against pertussis can be achieved by lowering the age of the first dose to one month (page 1162, 2nd col.). Halsey et al. also teaches the vaccination with a polio vaccine within the 42 day window (see Table 1).

12. Claims 2-4, 6-17, 19, 21, 23-33 and 34-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Jacob John (British Medical Journal 289:881-882,1984). New 56-100

John teaches the first dose of an oral poliomyelitis vaccine was given at day 7, 14, 21, 28, 35 or 42. John further suggests that the lower age limit for oral poliomyelitis vaccine should be 1 week and that the presence of maternal antibodies did not seem to inhibit the infant's ability to produce antibodies to the vaccine.

26, 27, 34-36, 38-41, 43, 44, 46, New 56-100

13. Claims 25-27, 34-36, 38-47, and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Chazono et al. (US 5,139,776).

Chazono et al. discloses a pertussis vaccine in a pharmaceutical formulation. This appears to

conform to the kit claims of the present invention in that it is killed vaccine in a pharmaceutical formulation.

Claim Rejections - 35 USC § 101

14. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van.Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 2-17, 19, 21, 23-33 and 34-55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-42 of Classen U.S. Patent No. 5,728,385 and claims 1-47 of Classen U.S. Patent No. 5,723,283. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the claims of the '385 patent are directed to a method of immunizing utilizing the same immunogens within the first 42 days of life. Similarly, the claims of the '283 patent are directed to a method of determining whether immunization within the first 42 days of life affects the incidence of chronic immune mediated disorders.

17. Certain papers related to this application may be submitted to Group 1643 by facsimile transmission. Papers may be faxed via the PTO Fax Center in Crystal Mall I. The faxing of such papers must conform with the notices published Official Gazette, 1096 OG 30 (October 19, 1988) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6 (d)). The Fax Center number is 703-305-3014. Note: If applicants do submit a paper by fax, the original signed copy should be retained by applicants or applicants' representative. No duplicate copies should be submitted so as to avoid the processing of duplicate papers in the Office.

18. Any inquiry concerning this communication or earlier communications should be directed to Jay Williams whose telephone number is 703-305-7141. The examiner can normally be reached Monday-Friday from 8 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can reached at 703-308-4311. Any inquiry of a general nature or relating to status of this application should be directed to the Group receptionist whose telephone number is 703-308-3891.

Jay F. Williams

October 1, 1998

Marian C Knode

MARIAN C. KNODE
SUPERVISORY PATENT EXAMINER
GROUP 1309